ADVANCED GLYCATION ENDPRODUCTS (AGEs) MODIFY ß-AMYLOID IN ALZHEIMER'S DISEASE BRAIN AND AFFECT ß-AMYLOID-MEDIATED TOXICITY

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Compared to non-diseased brains, we have found biochemical fractions of ß-amyloid plaques isolated from AD brains to contain more AGE-modifications (Vitek et al. PNAS 91:4766, 1994) and Smith et al. (PNAS 91: 5710, 1994) have localized AGE-immunohistochemical reactivity to AD plaques. We also find that the aggregation of soluble ßAP into fibrillar ß-amyloid is a nucleation-dependent process, and when nucleation seeds are reacted with glucose to form AGE-modified ßAP seeds, these modified seeds enhance the aggregation of ßAP compared to unmodified seeds. We have now tested whether the aggregates formed as a result of seeding are toxic. ß-amyloids composed of human ßAP 1-40 are toxic to PC12 and HTB14 cells in culture and when injected into rodent brains. In contrast, ß-amyloids composed of human ßAP 1-28 or of rodent ßAP 1-35 are not toxic. Thus, the possibility exists that a seed composed of toxic ßAP 1-40 may provide a template onto which rodent ßAP 1-35 may aggregate and that the resulting heterologous aggregate of human ßAP/rodent ßAP may differ in toxicity from its component parts. Rodent ßAP 1-35 was mixed with AGE-modified and non-modified seeds of human ßAP 1-40 and allowed to aggregate. We will discuss the results of our studies on these heterologous aggregates using FTIR, toxicity to cells in culture and by injection into rat brains.

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